

Research Paper

The Effects of Sodium Hydrosulfide on Motor Learning in a Rat Model of Parkinson's Disease



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ABSTRACT

Background Hydrogen Sulfide (H₂S), a novel endogenous gasotransmitter, plays an important role in neuromodulation and memory performance and also protects neurons against neurotoxin-induced neurodegeneration.

Objective This study aimed to investigate the potential neuroprotective effects of Sodium Hydrosulfide (NaHS), on motor learning in a unilateral 6-Hydroxydopamine (6-OHDA) rat model of Parkinson's Disease.

Methods Male Wistar rats were subjected to unilateral injection of 6-OHDA (15 µg) into the Medial Forebrain Bundle (MFB) and then treated with NaHS for 25 days. Animals were divided into control, sham, sham plus NaHS, Parkinson (6-OHDA), Parkinson plus vehicle (saline), and Parkinson plus NaHS (2.8 and 5.6 mg/kg, IP) groups, (N=8). One-way ANOVA followed by turkey's test was applied for statistical analyses of the data.

Findings The riding time in fixed and accelerating speed rotarod were significantly decreased in Parkinson rats (6-OHDA group) compared to controls in all training days (P<0.001). Treatment with NaHS (2.8 and 5.6 mg/kg/d) reversed these decreases in a dose-dependent manner, so no significant differences were found in these parameters between the control and Parkinson plus NaHS groups during the accelerating speed rotarod test.

Conclusion In the Parkinson rats, NaHS administration enhanced and improved the endurance time in the rotarod test. These results demonstrate that NaHS treatment enhances rat motor balance and coordination and suggest treatment with NaHS attenuates motor impairments in the Parkinson rats.

Extended Abstract

1. Introduction

Parkinson Disease (PD) is a progressive neurodegenerative disorder characterized by a progressive loss of Substantia Nigra pars compacta (SNc) dopaminergic neurons, which leads to motor symptoms of bradykinesia, rigidity, resting tremor, and postural imbalance [1].

PD is a neurodegenerative condition in which dementia may be observed even in the early stage of the disease together with mild motor disabilities that follows midbrain dopaminergic neuron loss [2].

The prevalence of cognitive dysfunction is high with reports indicating that this non-motor symptom negatively affects the quality of life of about 60% of patients with PD and cause morbidity and mortality in 36% of patients

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at the early onset of the disease [3]. Therefore, the patients suffering from PD, appear to be particularly susceptible to develop cognitive impairments 4-6 times more than what happens with normal aging [4].

Both structural and functional changes of the hippocampus which are involved in cognitive processes such as learning and memory have been observed in PD patients [5, 6]. Several studies have also shown that the reduction of hippocampal volume was accompanied by cognitive deficits in PD patients [7]. Numerous studies have suggested that neuroinflammation and oxidative stress play major roles in the pathogenesis of nigral dopaminergic cell death in PD [8].

6-Hydroxydopamine (6-OHDA) was the first dopaminergic neurotoxin used experimentally to induce PD [9]. The neuronal damage induced by 6-OHDA is mainly due to the great oxidative stress caused by the toxin. For this reason, unilateral injection of 6-OHDA is a good model for studying oxidative stress in the pathogenesis of PD. To date, three main gasotransmitters have been identified: Nitric Oxide (NO), Carbon monoxide (CO), and Hydrogen Sulfide (H_2S). It has been discovered that H_2S plays multiple functional roles in the body from cardiovascular tone regulation to neuromodulation.

In recent years, it has been demonstrated that H_2S as a cytoprotectant, significantly improves spatial learning and memory impairment induced by $A\beta$ and exerts anti-inflammatory, anti-apoptotic, and antioxidant effects [10]. However, the possible role of H_2S as an anti-antioxidant agent in cognitive dysfunction in a rat model of PD has not yet been fully elucidated. Therefore, the present study was designed to investigate the protective effects of H_2S against 6-OHDA-induced motor learning impairment in a unilateral 6-OHDA rat model of PD.

2. Methods and Materials

Animals were first anesthetized with Intraperitoneal (IP) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and were then placed in a stereotactic apparatus. Burr holes were drilled in the right side of the skull and 4 μ g of 6-OHDA mixed in 2 μ L of 0.2% ascorbic acid with 0.9% normal saline was injected into the ascending mesostriatal pathway using stereotactic positioning (4.4 mm posterior to the bregma, 1.2 mm lateral to the midline, and 7.8 mm below the dura) near the MFB at a rate of 0.2 μ L.

Administration of normal saline vehicle with the same volume was performed as sham surgery. Then the animals were divided into seven groups; including control, sham, sham plus NaHS (5.6 mg/kg), Parkinson (6-OHDA), Parkinson plus vehicle (saline), and Parkinson plus NaHS (2.8 and 5.6 mg/kg). Animals in the sham plus NaHS and 6-OHDA plus NaHS groups received daily intraperitoneal administration of NaHS (Sigma-USA) post-operation for 25 days. NaHS was dissolved in distilled water. Behavioral tests were performed 24 h after the last injection. Motor coordination was assessed using an automated rotating rod [11, 12]. One-way ANOVA was applied for statistical analyses of the data. The level of significance was less than 0.05.

3. Results

The overall results showed no statistically significant differences in different parameters between the sham, control, and sham plus NaHS groups. Furthermore, no statistically significant difference was found between the 6-OHDA and 6-OHDA plus vehicle (saline) groups with respect to different parameters. Data are not shown. Therefore, these data are not depicted graphically and the data obtained from the 6-OHDA plus saline (6-OHDA group) and 6-OHDA plus

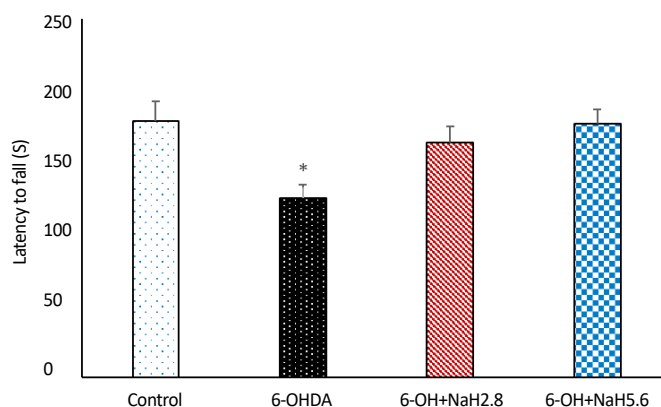


Figure 1. Comparison of latency to fall in control and experimental groups

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Effects of NaHS on 6-OHDA-induced impairment in motor learning of the rats in the rotarod test. All values are represented as Mean \pm SEM. * $P < 0.05$; Relative to the control group.

NaHS (2.8 and 5.6 mg/kg) groups were compared with each other and with the control group.

The riding time in fixed and accelerating speed rotarod significantly decreased in Parkinson rats (6-OHDA group) compared to controls, in all of the training days. Treatment with NaHS (2.8 and 5.6 mg/kg/d) reversed these decreases in a dose-dependent manner, so no significant differences were found between the control and Parkinson plus NaHS groups in these parameters during the fixed and accelerating speed rotarod test (Figure 1).

Our results showed that microinjection of 6-OHDA into the MFB depressed motor performances of animals on the rotarod and remarkably decreased the time that animals balanced steadily on the rotarod, whereas administration of NaHS (2.8 and 5.8 mg/kg) reversed the inhibitory effects of 6-OHDA on rotarod and considerably increased the animals' endurance time on rotarod. These results demonstrate that NaHS enhances rat motor balance and coordination in a unilateral 6-OHDA rat model of PD.

4. Conclusion

In the Parkinson rat group, NaHS administration enhanced and improved the endurance time in the rotarod test. These results demonstrate that NaHS treatment enhances rat motor balance and coordination and suggest that treatment with NaHS attenuates motor impairments in the Parkinson rat group.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Ethics Committee of the Qazvin University of Medical Sciences (code: IR.QUMS.REC.1396.476).

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Authors' contributions

Conception, design and revising the article critically for important intellectual content: Mohammad Hossein Esmacili; acquisition, Analysis and interpretation of data: Mohammad Hossein Esmacili, Esmacil Abbasi, Neda Farshad; and Drafting the article: Mohammad Hossein Esmacili, Hashem Haghdooost Yazdi.

Conflict of interest

The authors declared no conflict of interest.

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بررسی اثرات هیدروسولفید سدیم بر یادگیری حرکتی در مدل موش صحرایی پارکینسونی

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چکیده

زمینه: سولفید هیدروژن که نوعی ناقل گازی درون‌زای جدید است، نقش مهمی در تعدیل عصبی و حافظه دارد و از نورون‌ها در مقابل مواد سمی تخریب‌کننده محافظت می‌کند.

هدف: هدف از این مطالعه بررسی اثرات بالقوه محافظت نورونی هیدروسولفید سدیم بر یادگیری حرکتی در مدل موش پارکینسونی یک‌طرفه ۶-هیدروکسی دوپامین است.

مواد و روش‌ها: سم ۶-هیدروکسی دوپامین به صورت یک‌طرفه به ناحیه دسته مغز جلویی میانی تزریق شد و موش‌ها ۲۵ روز تحت درمان با هیدروسولفید سدیم قرار گرفتند. حیوانات به گروه‌های کنترل، شش، شش به همراه هیدروسولفید سدیم (۵/۶)، پارکینسونی و پارکینسونی به همراه سالین و هیدروسولفید سدیم ۵/۶ و ۲/۸ میلی گرم بر کیلوگرم تقسیم شدند (۸ رأس موش در هر گروه). برای مقایسه نتایج بین گروه‌ها از آزمون آماری آنوای یک‌طرفه و آزمون تعقیبی توکی استفاده شد.

یافته‌ها: استقامت در موش‌های گروه پارکینسونی در مقایسه با گروه کنترل به طور معنی‌داری در آزمون روتارود با سرعت چرخش ثابت و شتاب‌دار کاهش یافت ($P < 0.001$). درمان با هیدروسولفید سدیم این کاهش را به صورت وابسته به دوز معکوس کرده به گونه‌ای که هیچ تفاوت معنی‌داری در این متغیرها بین گروه کنترل و گروه پارکینسونی به همراه هیدروسولفید سدیم در طی آزمون روتارود با سرعت چرخش شتاب‌دار مشاهده نشد.

نتیجه‌گیری: تزریق هیدروسولفید سدیم به موش‌های پارکینسونی، باعث بهبود و افزایش زمان استقامت در آزمون روتارود آن‌ها شد که نشان می‌دهد هیدروسولفید سدیم موجب تقویت هماهنگی حرکتی می‌شود و می‌تواند اختلالات حرکتی را در موش‌های پارکینسونی کاهش دهد.

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